Title Page

Protocol Title:

A parallel-group, randomized, prospective, interventional, double-blind, multicenter global Phase 3 study to investigate the efficacy and safety of finerenone versus placebo, in addition to standard of care, in participants with chronic kidney disease and type 1 diabetes

Protocol Number:	22267
Protocol Version:	2.0
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Compound Number:	Finerenone (BAY 94-8862)
Short Title:	Effects of ***fine***renone on the efficacy and safety in chronic kidney disease and type ***1*** diabetes
Study Phase:	3
Acronym:	**FINE-ONE**

Sponsor Name: Bayer AG

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Document History Table

DOCUMENT HISTORY			
Document	**Version**	**Date**	**Comments (if applicable)**
Amendment 1	2.0	23 OCT 2023	Global amendment that includes changes due to health authority expectations applicable to all countries.
Clinical Study Protocol	1.0	08 MAY 2023	

Protocol Amendment Summary of Changes

Amendment 1 (23 OCT 2023)

This amendment/modification is considered to be substantial based on the relevant criteria of the European Union clinical trial legislation.

Overall Rationale for the Amendment:

This amendment is prepared to implement changes expected by various Health Authorities.

Below is a description of the changes and brief rationales.

Section # and Name	Description of Change	Brief Rationale
3 Objectives, Endpoints, and Estimands 9.3.2.2 Intercurrent Event Strategy for the Primary Efficacy Estimand	Adapted text on the imputation for the worst case scenario to handle ICEs: change in UACR from baseline.	Following a request from the FDA.
5.1 Inclusion Criteria	For inclusion criterion number 8, it was added that participants not capable of giving signed informed consent will not be enrolled into the clinical trial.	Following a request from EMA within the EU CTR process.
7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal 8.4 Adverse Events (AEs), Serious Adverse Events (SAEs) and Other Safety Reporting 10.1.3 Informed Consent Process	Deletion of mentioning an authorized representative in all subsections.	Following a request from EMA within the EU CTR process and in line with the clarification regarding the inclusion criterion on informed consent, any reference to an authorized representative was deleted throughout the protocol.
6.4 Blinding	Clarified that any unblinding decision must not be delayed due to contacting the sponsor.	Following a request from the Medicines and Healthcare products Regulatory Agency (MHRA).

Section # and Name	Description of Change	Brief Rationale
7.1.1 Permanent Discontinuation of Study Intervention	Clarification regarding additional telephone contacts, that other contacts as provided by the participant will only be used where permissible per local regulations.	Following a request from EMA within the EU CTR process.
9.3.5 Other Analyses	Section added to pre-specify relevant subgroups.	Following a request from the FDA.
10.7.1 China (CHN)	Names of the central laboratory and the central sample destruction facilities added.	To meet China Human Genetic Resources Administration Office (CHGRAO) expectation to reference the names of the central laboratory and the central sample destruction facilities in China.

In addition, minor editorial revisions have been made throughout the document.

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List of Abbreviations and Definitions of Terms

In general, abbreviations are not introduced in the text but are listed here only.

ACEI	Angiotensin-converting enzyme inhibitor
AE	Adverse event
AESI	Adverse event of special interest
ANCOVA	Analysis of covariance
ARB	Angiotensin receptor blocker
BP	Blood pressure
CFR	Code of Federal Regulations
CHGRAO	China Human Genetic Resources Administration Office
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case report form
CT	Clinical Trials
CV	Cardiovascular
CYP3A4	Cytochrome P450 isoenzyme 3A4
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
ESRD	End stage renal disease
EU	European Union
EU CTR	European Union Clinical Trials Regulation
FAS	Full analysis set
FDA	Food and Drug Administration
FIDELIO-DKD	**FI**nerenone in reducing ki**D**n**E**y fai**L**ure and d**I**sease pr**O**gression in **D**iabetic **K**idney **D**isease (Study 16244)
FIDELITY	Preplanned pooled analysis of FIDELIO-DKD and FIGARO-DKD
FIGARO-DKD	**FI**nerenone in reducin**G** c**A**rdiovascular mo**R**tality and m**O**rbidity in **D**iabetic **K**idney **D**isease (Study 17530)
FINE-ONE	**FINE**renone in Type **ONE** diabetes
FSH	Follicle stimulating hormone
FU	Follow-up
GCP	Good Clinical Practice
GLP1	Glucagon-like peptide-1
HbA1c	Hemoglobin A1c
HRT	Hormonal replacement therapy
IB	Investigator's Brochure

ICE	Intercurrent event
ICF	Informed consent form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
MedDRA	Medical Dictionary for Regulatory Activities
mIU/mL	Milli-international units per milliliter
MHRA	Medicines and Healthcare products Regulatory Agency
MR	Mineralocorticoid receptor
MRA	Mineralocorticoid receptor antagonist
NT-proBNP/BNP	N-terminal prohormone B-type natriuretic peptide/ B-type natriuretic peptide
OD	Once daily
PD	Premature discontinuation
PK	Pharmacokinetics
PV	Pharmacovigilance
QTL	Quality tolerance limit
RND	Randomization
SAE	Serious adverse event
SAF	Safety Analysis Set
SAP	Statistical analysis plan
SCr	Standardized serum creatinine
SD	Standard deviation
SGLT	Sodium-Glucose co-transporter
SoA	Schedule of activities
SoC	Standard of care
SUSAR	Suspected unexpected serious adverse reaction
T1D	Type 1 diabetes
T2D	Type 2 diabetes
TE	Treatment-emergent
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
UACR	Urinary albumin-to-creatinine ratio
US(A)	United States (of America)
WGS	Whole genome sequencing
WOCBP	Woman of child bearing potential
WONCBP	Woman of non-childbearing potential

1. Protocol Summary

1.1 Synopsis

Protocol Title:

A parallel-group, randomized, prospective, interventional, double-blind, multicenter global Phase 3 study to investigate the efficacy and safety of finerenone versus placebo, in addition to standard of care, in participants with chronic kidney disease and type 1 diabetes

Short Title:

Effects of ***fine***renone on the efficacy and safety in chronic kidney disease and type ***1*** diabetes

Regulatory Agency Identifier Numbers:

Registry	ID
EU CT:	2022-503024-27-00
US IND:	163802

Envisaged indication: Chronic kidney disease associated with type 1 diabetes mellitus

Rationale:

The aim of this study is to demonstrate efficacy of finerenone when compared to placebo, in addition to SoC, in delaying the progression of CKD in participants with CKD and T1D as there is an unmet medical need for an approved treatment for these patients.

Efficacy will be shown based on UACR that is used as a bridging biomarker to demonstrate slowing of kidney disease progression and to support regulatory approval. UACR can serve as a bridging biomarker given the shared underlying cause of CKD, the strong association of albuminuria with kidney disease progression in both types of diabetes and the robust body of evidence of efficacy of finerenone on clinical renal outcomes in patients with CKD and T2D. It is expected that finerenone will also reduce UACR in CKD and T1D which will translate into reducing CKD progression in patients with T1D (see Section 4.2 for more details).

Objectives, Endpoints, and/or Estimands:

Table 1–1: Summary of primary and secondary study objectives and endpoints

Objectives	Endpoints
Primary efficacy	**Primary endpoint**
• To demonstrate that finerenone in addition to SoC is superior to placebo in reducing UACR over 6 months when compared to placebo in participants with CKD and T1D	○ Change in UACR from baseline (ratio to baseline) over 6 months
The primary clinical question of interest is to demonstrate a difference between assigning finerenone and placebo, for which pre-specified attributes of the primary estimand will be considered.	
Secondary safety	**Secondary endpoints**
• To assess the safety of finerenone in addition to SoC compared to placebo	○ Number of participants with ○ TEAEs, TESAEs ○ Hyperkalaemia (AESI)

AESI = adverse event of special interest, CKD = chronic kidney disease, SoC = Standard of care, T1D = type 1 diabetes, TEAE = treatment-emergent adverse events, TESAE = Treatment-emergent serious adverse event, UACR = Urinary albumin-to-creatinine ratio

Overall Design Synopsis:

FINE-ONE (study 22267) is a multicenter, international, randomized, placebo-controlled, double blind parallel-group Phase 3 study.

Participants who fulfill all eligibility criteria will be randomized in a 1:1 ratio to receive finerenone or placebo. All participants will receive blinded study intervention on top of standard of care, i.e. either an ACEI or an ARB.

UACR as the primary endpoint measure and serum potassium as the key safety parameter will be assessed according to the visit schedule.

An optional pre-screening visit may be performed, to identify potential participants prior to main study consent. Visits will take place at screening, baseline (randomization at Day 1), Month 1, Month 3 and Month 6 (the planned end of study intervention) and at the Follow-up 30 days after last dose of study intervention. Additional safety visits will take place 4 weeks (± 7 days) after each up-titration or after restart of study intervention following treatment interruption for >7 days.

Participants permanently discontinuing study intervention should attend a Premature Discontinuation visit and a Follow-up visit and then continue with all remaining protocol specified study visits up to Month 6 visit.

Steering and Data Monitoring Committees are in place to ensure scientific integrity, oversight and ongoing safety monitoring.

Number of Participants:

Approximately 440 participants will be screened to achieve 220 participants randomly assigned to study intervention.

Study Arms and Duration:

The following intervention arms are included in the study:

- Finerenone (10 mg or 20 mg OD), the sponsor's study intervention under investigation
- Placebo, the study intervention used as comparator.

The starting dose will depend on the participant's eGFR level at the Screening Visit: a lower dose of 10 mg OD if eGFR is ≥25 to <60 mL/min/1.73 m^2, or the higher (target, maximum)

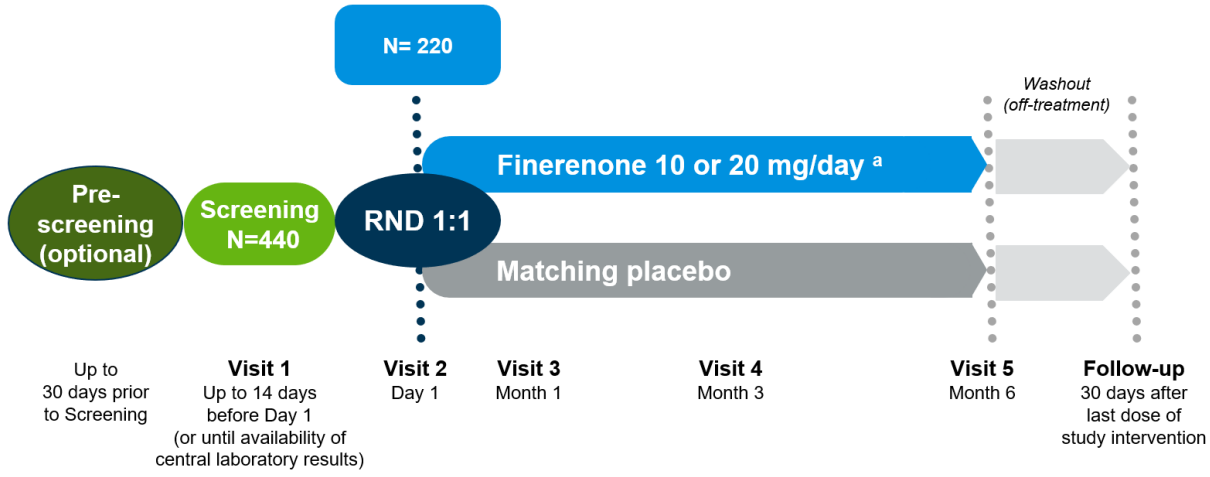
dose of 20 mg OD if eGFR is ≥60 mL/min/1.73 m^2. Participants who start on the lower dose of 10 mg will be up-titrated to the target dose of 20 mg from Month 1 on treatment onwards provided potassium is ≤4.8 mmol/L, and eGFR decrease is less than 30% of the last measured value. Up- and down-titration of study intervention will be based on local potassium and eGFR values. Rules for temporary or permanent discontinuation and dose adjustment of study intervention are based on potassium values and eGFR (see Sections 6.1 and 6.6).

Study Periods	Duration
Screening	Up to 14 days (or until availability of central lab results)
Intervention	6 months
Follow-up	1 month
Total study duration	approximately 7.5 months (not considering optional pre-screening)

Data Monitoring/Other Committee: Yes

1.2 Schema

Figure 1–1: Study Schema



eGFR = estimated glomerular filtration rate, N = number of participants, RND = randomization

a Starting dose of finerenone:
10 mg/day for eGFR ≥25 to <60 mL/min/1.73 m² or
20 mg/day for eGFR ≥60 mL/min/1.73 m² at Screening visit

1.3 Schedule of Activities (SoA)

Procedure	Pre-screening	Screening [a]	Intervention period				4-week Safety visit	Premature [b] discontinuation	Follow-up
Day/Month	**Up to 30 days prior to Screening**	**Up to 14 days before Day 1**	**Day 1 [a] (Baseline)**	**Month 1**	**Month 3**	**Month 6**	**28 days** post up-titration or reinitiation	**As soon as possible** after last study intervention intake	**30 days** after last dose of study intervention
Visit window				±7	±7	±7	±7	within 14 days	±7
Visit number/name	**Optional**	**V1 [a]**	**V2 [a]**	**V3**	**V4**	**V5**	**Unscheduled**	**PD [b]**	**FU**
			Informed consent and eligibility check						
Pre-screening consent	X								
Informed consent		X							
Inclusion/ exclusion criteria		X	X						
			Baseline characteristics						
Demographics		X							
Full physical examination			X						
Medical history		X							
Prior medication		X							
Randomization				X					
			Central laboratory evaluations / efficacy						
Urinalysis: Central UACR	X	X	X		X	X		X	X
			Laboratory evaluations (central or local)						
Local: Pregnancy test (if WOCBP)		X	X						
Central: Limited Chemistry: HbA1c		X	-		-	X	X		-	-
eGFR, serum K^+, uric acid, Na^+		X	X		X	X	X		X	X
Local: Serum K^+		X	X		X	X		X		
Local: eGFR			X		X	X		X		
Biomarker sample (not relevant for China)		X	X		X	X	X			X
Genetic sample (not relevant for China)			X							
			Further safety evaluations and Study intervention						
12-lead ECG			X						
Vital signs (blood pressure, heart rate)		X	X		X	X	X	X	X	X
Height, body weight		X					X			
Study intervention dispensation/ administration and accountability				X	X	X	X		X	
AE/SAE/concomitant medication review		← ----------	←==========							→→

Annotated Schedule of Activities

Informed consent and eligibility check	
Informed consent	Main informed consent (including consent for biomarkers) may be performed up to 30 days in advance of the Screening visit. Informed Consent for optional whole genome sequencing will be provided separately and could be done at Visits 1 or 2.
Inclusion/ exclusion criteria	At Visit 2 a re-check has to be done prior to randomization.
Laboratory evaluations / efficacy	
Urinalysis: Central UACR	For collection of morning void urine samples see Section 8.2. The value at Screening is to be used for eligibility check (1 reassessment is allowed).
Laboratory evaluations	
Pregnancy test (if WOCBP)	Negative pregnancy test (serum, plasma or urine according to local regulations) at Screening (Section 8.3.5). At Day 1 (Visit 2, before intake of study intervention) a repeat test is required, unless ≤4 days lie between Screening and first intake of study intervention. If required by local regulations, pregnancy tests have to be done at any of the visits thereafter.
Central: Limited Chemistry HbA1c, eGFR, serum K^+, uric acid, Na^+	At Screening:- HbA1c for eligibility check (1 reassessment is allowed in case 1st measurement is missing/unreadable/invalid) - eGFR for eligibility check (1 reassessment is allowed) and assignment to starting dose of study intervention at Day 1. Uric acid and serum sodium will not be analyzed at Screening.
Local: Serum K^+	Values will be used for dose adjustments of study intervention (Sections 6.1 and 6.6). The value at Screening is to be used for eligibility check (1 reassessment is allowed).
Local: eGFR	Values will be used for dose adjustments of study intervention (Section 6.1).
Biomarker sample	Serum or plasma and urine samples (see Section 8.8). Urine samples will be taken from the morning void samples collected for urinalysis, i.e. not for Month 1 (Visit 3) where no urine sample will be collected.
Genetic sample	Whole blood sample (Section 8.7). Can be taken also on Visit 3.
Further safety evaluations and Study intervention	
12-lead ECG	If clinically indicated, to be done also at later timepoints (e.g. serum K+>6.5 mmol/L) (Section 8.3.3).
Height, body weight	Height will be recorded at Screening only.
Study intervention dispensation/ administration and accountability	At Day 1, the first study intervention intake will be at the site. At Month 6 or PD visits, no dispensation and administration will take place.
AE/SAE/concomitant medication review	AE/SAE will be documented from start of study intervention until the last visit; only study procedure related events will be reported from signing of Informed consent onwards (Section 8.4.1).

1 month is counted as 28 days.

For country-specific requirements refer to Section 10.7.

AE = adverse event, ECG = electrocardiogram, eGFR = estimated glomerular filtration rate, FU = follow-up, HbA1c = glycated hemoglobin, K^+ = potassium, PD = Premature discontinuation, SAE = serious adverse event, UACR = urine albumin-to-creatinine ratio, V = Visit, WOCBP = women of child-bearing potential

a) Screening window begins on the first day of the Screening visit performed by the investigator; urine collection (Section 8.2) may be started prior to the Screening visit. Participants can be randomized outside of the screening window if central laboratory samples are taken but pending results. Once all laboratory results have been reviewed by the investigator, participant eligibility may be confirmed. All screening procedures/assessments must be completed before randomization occurs.
X for Day 1 (Visit 2) on the left part indicate procedures that have to be done before randomization.
In the exceptional case where no previous evidence of albuminuria is documented in the participant's medical records, the pre-screening UACR value can be used instead. In such situations, the Screening visit can only take place at least 3 months after pre-screening.

b) Participants who prematurely discontinue study intervention permanently are expected to attend the PD and then the FU visit and then continue with all remaining protocol specified study visits up to the Month 6 visit. In case of >14 days after last study intervention intake the participant would directly perform the Follow-up visit (without the PD visit), followed by the remaining protocol specified study visits up to the Month 6 visit.

2. Introduction

Finerenone (BAY 94-8862) is an oral, selective, non-steroidal MRA that is being developed for once daily treatment of CKD and T1D.

2.1 Study Rationale

The aim of this study is to demonstrate efficacy of finerenone when compared to placebo, in addition to SoC, in delaying the progression of CKD in participants with CKD and T1D as there is an unmet medical need for an approved treatment for these patients.

Efficacy will be shown based on UACR that is used as a bridging biomarker to demonstrate slowing of kidney disease progression and to support regulatory approval. UACR can serve as a bridging biomarker given the shared underlying cause of CKD, the strong association of albuminuria with kidney disease progression in both types of diabetes and the robust body of evidence of efficacy of finerenone on clinical renal outcomes in patients with CKD and T2D. It is expected that finerenone will also reduce UACR in CKD and T1D which will translate into reducing CKD progression in patients with T1D (see Section 4.2 for more details).

2.2 Background

T1D is a chronic autoimmune disorder characterized by destruction of pancreatic beta cells leading to insulin deficiency and requiring lifelong insulin treatment (Thomas et al. 2018). Among the US population overall, crude estimates for 2018 indicated that 1.4 million adults aged 20 years or older (or 5.2% of all US adults with diagnosed diabetes), reported both having T1D and using insulin (Centers for Disease Control and Prevention 2020).

CKD affects up to 40% of people with T1D and 25% of those progress to ESRD. In a systematic analysis for the Global Burden of Disease study, it was reported that the prevalence of CKD due to T1D had increased by 58.2% from 1990 to 2007 and by 21.7% from 2007 to 2017. The 2017 global prevalence of CKD due to T1D was an estimated 32.5 per 100,000 individuals (GBD Collaborators 2018).

In an analysis of the National Health and Nutrition Examination Surveys (NHANES) database conducted by Bayer 258,196 adult patients (95% confidence interval 71,189-445,203) were estimated to have T1D and CKD in the US between 2015 and 2018 (data on file).

The clinical course of CKD in patients with T1D is characterized by an increased urinary albumin excretion rate, which is the first sign of kidney damage and may progress to macroalbuminuria and decrease in eGFR in later stages (Groop et al. 2009).

The treatment of T1D consists of insulin treatment to control hyperglycemia. In patients with T1D, blood glucose intervention targeting HbA1c levels ≤7% can slow onset and progression of kidney disease. ACEIs and ARBs are to be initiated in patients with T1D, hypertension, and albuminuria (de Boer et al. 2022). Despite these guideline-recommended treatments, residual risk remains high in patients with CKD and T1D with up to a quarter progressing to end-stage-kidney-disease and CKD disease being a leading cause of mortality in T1D (Bjornstad et al. 2014).

Finerenone is a non-steroidal, selective antagonist of the MR, which is activated by aldosterone and cortisol and regulates gene transcription. Finerenone blocks MR-mediated sodium reabsorption and MR overactivation in both epithelial (e.g., kidney) and nonepithelial (e.g., heart and blood vessels) tissues. Overactivation of MR is thought to contribute to fibrosis and inflammation.

Finerenone's efficacy and favorable safety profile has been well described based on over 6,500 patients with CKD and T2D treated with finerenone in the FIDELIO-DKD and FIGARO-DKD studies, as shown in the pooled FIDELITY analysis (Agarwal et al. 2022). Finerenone consistently showed a reduction in UACR at Month 4, which remained sustained thereafter. Along with the early reduction in albuminuria, finerenone has demonstrated to significantly slow the progression of CKD and reduce the risk of cardiovascular events across a broad range of T2D and CKD severities on top of either ACEI or ARB treatment (see also Section 4.2). Currently, finerenone (10 mg and 20 mg tablets) has been approved for CKD in T2D and is being marketed globally.

A detailed description of the chemistry, pharmacology, efficacy, and safety of finerenone is provided in the Investigator's brochure and the package insert.

2.3 Benefit/Risk Assessment

2.3.1 Risk Assessment

Due to the pharmacological mode of action, finerenone is associated with an increased risk of hyperkalemia which was also identified from previous studies with finerenone. In the Phase 3 FIDELIO-DKD and FIGARO-DKD studies in participants with CKD and T2D, hyperkalemia increased approximately two-fold with finerenone treatment (18.3% finerenone vs. 9.0% placebo in FIDELIO-DKD; 10.8% finerenone vs. 5.3% placebo in FIGARO-DKD). In both studies, most treatment-emergent hyperkalemia events were non-serious, mild or moderate in intensity, and had resolved. There were no fatal hyperkalemia treatment-emergent AEs. Treatment-emergent hyperkalemia AEs of relevant clinical consequence constituted a small proportion (i.e., those leading to permanent study intervention discontinuation in 2.3% finerenone vs. 0.9% placebo in FIDELIO-DKD and 1.2% vs. 0.4% in FIGARO-DKD or hospitalization in 1.4% vs. 0.3% in FIDELIO-DKD and 0.6% vs. <0.1% in FIGARO-DKD). Further, there was no evidence for an increased incidence of any severe clinical cardiac manifestations of hyperkalemia (e.g., bradycardia, ventricular arrhythmia, or sudden cardiac death) in either study (Bakris et al. 2020, Pitt et al. 2021). Overall, in participants with CKD and T2D the risk of hyperkalemia was manageable.

The population in this study 22267 has an inherent risk of hyperkalemia due to their CKD (as serum potassium tends to increase with decreasing eGFR) and due to standard of care therapy (ACEI/ARB) (Bianchi and Regolisti 2019). Thus, to minimize the risk of hyperkalemia, potassium levels will be closely monitored, starting doses of study intervention will be chosen according to baseline renal function, and subsequent dose up-titration will be performed on the basis of measured potassium and eGFR values. Stopping rules for temporary and permanent discontinuation or dose reduction of study intervention based on potassium values will minimize the risk of hyperkalemia. At any time during the study, the investigator has the option to also down-titrate the study intervention, depending on serum potassium and the progression of the underlying disease (see Section 6.6).

2.3.2 Benefit Assessment

Apart from contributing to the process of developing a new therapy in an area of unmet need, a participant in this study 22267 may derive general medical benefit from careful and close monitoring by medical personnel during the entire course of the study.

Despite guideline recommended standard of care, 25% of patients with CKD and T1D are progressing to ESRD and are consistently observed to have substantially elevated mortality rates (Bjornstad et al. 2014). Albuminuria and eGFR are independently and additively associated with kidney function decline and increased risks of CV events, CV mortality, and all-cause mortality (Toyama et al. 2013). There is a high unmet medical need for treatments that can slow the progression of kidney disease in patients with T1D and as well reduce the associated burden of CV morbidity and mortality.

In the Phase 3 FIDELIO-DKD and FIGARO-DKD studies in participants with CKD and T2D, finerenone in addition to SoC reduced the risk of clinical renal outcomes and lowered UACR. As the disease processes driving CKD in both T2D and T1D are closely related and there is a biological plausibility that albuminuria captures effects of principal causal pathways through which clinical outcomes are affected, UACR will be used as a bridging biomarker between CKD in T2D and CKD in T1D to show renal efficacy. In this study 22267, reduction of albuminuria measured within 6 months, is believed to translate into the clinical benefit of slowing of kidney disease progression for those participants assigned to finerenone (see also Section 4.2).

2.3.3 Overall Benefit: Risk Conclusion

Considering the high unmet medical need in patients with CKD and T1D, the anticipated benefits in light of the available preclinical and clinical data and the manageable risk of hyperkalemia, the benefit risk assessment of finerenone for the inclusion of participants into the study is considered positive and in favor of participating in this study.

3. Objectives, Endpoints, and Estimands

Primary efficacy and **secondary safety objectives** are reported together with the respective **primary** and **secondary endpoints** and the **primary estimand** of the study (Table 3–1). This table also summarizes pre-specified **exploratory objectives (efficacy, biomarkers)** and the respective **other exploratory endpoints.**

Table 3–1: Study objectives and endpoints

Objectives	Endpoints
Primary	
Efficacy	**Primary endpoint**
• To demonstrate that finerenone in addition to SoC is superior to placebo in reducing UACR over 6 months in participants with CKD and T1D	• Change in UACR from baseline (ratio to baseline) over 6 months
The ***primary clinical question of interest*** is to demonstrate a difference between assigning finerenone and placebo including effects of death and ESRD and irrespective of treatment discontinuation. Assuming a beneficial effect of finerenone after 6 months of treatment, using the treatment policy strategy is considered to produce a conservative estimate of the average effect that might be seen in clinical practice. In detail, the attributes constituting the **primary estimand** are the following: o *Population:* Adults with a clinical diagnosis of CKD and T1D. o *Treatment:* Finerenone (10 mg or 20 mg) or placebo on top of protocol defined background therapy o *Endpoint:* see primary endpoint above o *Intercurrent events and strategy:* The most important ICEs are death and ESRD: These events are considered clinically relevant and will be handled using a composite strategy. Therefore, the treatment effects that are observed will be assessed on the primary outcome and the ICEs. A “worst case” approach will be implemented to handle the ICEs in terms of a composite strategy. For participants experiencing the ICE, their subsequent UACR values will be set to a “worst case” value. Given there is no upper limit for post-baseline UACR measurements, the values will be drawn from the distribution of the largest change in UACR from baseline values observed during the trial (e.g. worst 10% of change in UACR from baseline values). Multiple imputation methodology will be adapted for this to avoid underestimation of the standard error. Treatment policy strategy relates to participants being followed up for the remainder of the study after discontinuing study intervention for reasons other than death or ESRD. Follow-up time after discontinuation of study intervention will be included in the analysis. o *Population-level summary:* Geometric mean ratio of treatment arm ‘ratios to baseline’ over the study period (i.e. average of geometric mean of treatment effect at Month 3 and Month 6 visits).	
Secondary	
Safety	**Secondary endpoints**
• To assess the safety of finerenone in addition to SoC compared to placebo	• Number of participants with o TEAEs, TESAEs o Hyperkalaemia (AESI)
Exploratory	**Other exploratory endpoints**
Efficacy	
• To further demonstrate the effect of finerenone in addition to SoC as compared to placebo	• Proportion of participants with ≥30% reduction of UACR from baseline at Month 6 • Proportion of participants with ≥50% reduction of UACR from baseline at Month 6 • Change in UACR from baseline to Month 3 • Change in UACR from baseline to Month 6

(continued)

Table 3–1: Study objectives and endpoints

Objectives	Endpoints
Exploratory	**Other exploratory endpoints**
Biomarkers	
• To further investigate the study intervention (e.g., mode-of-action-related effects, safety) and to further investigate pathomechanisms deemed relevant to renal and cardiovascular disease - including diabetes - and associated health problems.	• Various biomarkers (e.g., diagnostic, safety, pharmacodynamic, monitoring, or potentially predictive biomarkers)

AESI = adverse event of special interest, CKD = chronic kidney disease, ICE = intercurrent event, SoC = Standard of care, T1D = type 1 diabetes, TEAE = treatment-emergent adverse events, TESAE = Treatment-emergent serious adverse event, UACR = Urinary albumin-to-creatinine ratio

4. Study Design

4.1 Overall Design with Screening, Study Intervention and Follow-up

This is a double blind parallel-group intervention study in CKD and T1D patients (for an overview see the study scheme in Figure 1–1). UACR as the primary endpoint measure and serum potassium as the key safety parameter will be assessed according to the visit schedule (SoA in Section 1.3). The study was designed by Bayer and the Steering Committee. The independent Steering Committee will ensure scientific integrity and the Data Monitoring Committee will perform ongoing safety monitoring (see Section 10.1.6).

Pre-screening (optional)

An assessment of UACR to identify potential participants prior to the main study consent is permitted under the Pre-screening visit and will be assessed at the central laboratory. Participants will be required to provide a separate informed consent for this UACR test, and very limited data will be reported (see SoA in Section 1.3). The Pre-screening is optional and may be performed if the investigator wishes to obtain a recent UACR value (one sample, preferably morning void) to help assess if a participant is likely to be eligible. The pre-screening UACR value cannot be used in lieu of the centrally assessed urinalysis at Screening.

In the exceptional case where no previous evidence of albuminuria is documented in the participant's medical records, the pre-screening value can be used instead. In such situations, the screening visit can only take place at least 3 months after pre-screening.

Screening

Approximately 440 participants will be screened to achieve 220 participants randomly assigned to study intervention.

Baseline with randomization at Day 1

Participants who fulfill all eligibility criteria (see Sections 5.1 and 5.2) will be randomized in a 1:1 ratio to receive either finerenone or placebo at Day 1.

Intervention period

All participants will receive blinded study intervention (i.e. finerenone 10mg/20mg or placebo) OD on top of SoC, i.e. either an ACEI or an ARB.

The starting dose will depend on the participant's eGFR level (CKD-EPI 2009, Section 10.2) at the Screening visit: a lower dose of 10 mg OD if eGFR is ≥25 to <60 mL/min/1.73 m^2, or the higher (target, maximum) dose of 20 mg OD if eGFR is ≥60 mL/min/1.73 m^2. Participants who start on the lower dose of 10 mg will be up-titrated to the target dose of 20 mg from Month 1 onwards provided potassium is ≤4.8 mmol/L, and eGFR decrease is less than 30% below the value at the last scheduled visit. Up- and down-titration of study intervention will be based on local potassium and eGFR values (for details see Section 6.1).

The planned 6-month intervention period per participant starts with intake of the first dose of study intervention (after randomization) on Day 1 and includes visits at Month 1, Month 3 and Month 6. Additional safety visits will take place 4 weeks (± 7 days) after each up-titration or after restart of study intervention following treatment interruption for >7 days.

Month 6

- End of treatment visit for participants with the planned intervention period of 6 months
- End of study visit for participants who prematurely discontinue study intervention permanently (see PD visit below).

Follow-up (FU)

The FU visit will take place approximately 30 days after last administration of study intervention.

Permanent Discontinuation of Study intervention (PD visit)

Participants who prematurely discontinue study intervention permanently are expected:

- To attend the PD visit followed by the FU visit and then continue with all remaining protocol specified study visits up to the Month 6 visit, which would be their last study visit
- Only if more than 14 days have passed from the last study intervention intake:
  To directly perform the FU visit (without the PD visit), and then continue with all remaining protocol specified study visits up to the Month 6 visit.

4.2 Scientific Rationale for Study Design

The intervention model of the study includes assignment of oral finerenone in a double-blind setting intended to assess the efficacy and safety of finerenone in participants with CKD and T1D. Like in previous finerenone trials, participants and investigators will be blinded to study intervention allocation ensuring a double-blind design, thus limiting bias.

The use of placebo is for incorporating an inert control arm. This permits to quantify the extent to which the responses and side effects may be connected to the pharmacologic activity of the drug being studied and the proportion to which the responses may be linked to alternative factor (Sanderson et al. 2013).

The primary objective of the study is to demonstrate that finerenone on top of SoC is superior to placebo in reducing UACR over 6 months in participants with CKD and T1D.

UACR is a measurement of albuminuria, a predictor of long-term renal and CV adverse outcomes in T2D patients (Fox et al. 2012, Heerspink et al. 2019). Post-hoc analyses of randomized clinical trials suggest that a meaningful reduction in albuminuria may translate to protection from declining renal function and CV events in patients with diabetic kidney disease (Heerspink et al. 2014, Levey et al. 2020). For every 30% reduction in albuminuria, one can expect the risk of ESRD to be decreased by 23.7% (95% confidence interval 11.4%-34.2%; p=0.001) (Heerspink and Gansevoort 2015). Changes in UACR can be detected early in response to treatment.

In this study albuminuria is used as a primary endpoint in a bridging biomarker approach (Fleming et al. 2023), as there is biological plausibility that UACR captures effects of principal causal pathways through which clinical outcomes are affected and the disease processes driving CKD in both T2D and T1D are closely related (Papadopoulou-Marketou et al. 2017). Furthermore albuminuria is a marker of severity of kidney injury and is strongly associated with progression of kidney diseases in both T1D and T2D (Berhane et al. 2011, de Boer and Group 2014). Similarity of response to reduction of UACR translating into clinical benefits in both T1D and T2D populations was shown for other drugs affecting the renin-angiotensin-aldosterone-system system like ACEIs (Brenner et al. 2001, Lewis et al. 1993).

Substantial evidence of safety and effectiveness was demonstrated for finerenone in the two Phase 3 studies FIDELIO-DKD and FIGARO-DKD in patients with CKD and T2D (Bakris et al. 2020, Pitt et al. 2021) that resulted in approval of finerenone in CKD and T2D. In these studies, finerenone reduced the risk of renal and CV events and led to an early and persistent reduction in UACR. Finerenone showed benefits on renal outcomes in FIDELIO-DKD and FIGARO-DKD (Agarwal et al. 2022) with a significant proportion of the treatment effect (83%) attributed to the effect on UACR reduction at Month 4 (data on file).

UACR reduction will be used as a bridging biomarker between the study data available in patients with CKD in T2D and the upcoming data of the FINE-ONE study in participants with CKD in T1D. There is evidence that reduction of UACR at Month 6 correlates with delaying kidney disease progression, and therefore UACR at Month 6 is considered an appropriate endpoint for efficacy assessment in this study.

Finerenone's safety profile was well characterized for patients with CKD and T2D through its Phase 2 and Phase 3 studies. In both Phase 3 studies, the incidence of hyperkalemia was elevated but the clinical events were mostly mild to moderate, discontinuations of study intervention or hospitalization due to hyperkalemia were low in the finerenone groups, and there were no deaths due to hyperkalemia. Furthermore, finerenone did not alter HbA1c or glucose levels compared to placebo (Agarwal et al. 2022). There is no reason to assume increased risk of side effects or adverse events in patients with CKD in T1D compared to T2D. Factors that drive hyperkalemia risk, like high baseline potassium and low baseline eGFR are considered in the study design. An upper threshold of potassium (4.8 mmol/L) and eGFR ≥25 mL/min/1.73 m^2 for study inclusion as well as guidance on up- and down-titration of study intervention based on potassium and eGFR have been chosen for this study as confirmed effective and safe in the FIDELIO-DKD and FIGARO-DKD studies.

4.3 Justification for Dose

Doses of 10 mg and 20 mg have been confirmed to be effective and safe in the FIDELIO-DKD and FIGARO-DKD trials. As per label for the approved indication of CKD and T2D, the participants in this study will start the treatment with finerenone (or matching placebo) at a dose of 10 mg or 20 mg OD, depending on the participant's eGFR level at the Screening. Potassium and eGFR values obtained from local laboratory will be used for finerenone up-/down-titration as well as monitoring after down/up-titration and restarting the study intervention if interrupted.

4.4 End-of-Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study globally.

The primary completion date is defined as the date of the last on-treatment visit of the last participant in the study globally.

A participant is considered to have completed the study if he/she has completed all phases of the study, including the last visit.

5. Study Population

The study will enroll adults with CKD and T1D.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Participant must be ≥18 years of age (or the legal age of consent according to local legislation) at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Participants with T1D, i.e.
   T1D continuously treated with insulin, started within one year from diagnosis.

   If the onset was after age 35, documentation of the presence of one or more of the following:

   - Documented presence of circulating T1D-associated autoantibodies
   - History of hospitalization for diabetic ketoacidosis
   - Documented plasma C-peptide below the limit of detection with standard assay (with concurrent blood glucose >100 mg/dl).
3. HbA1c at Screening <10% (central assessment).
   - Note: One reassessment is allowed for HbA1c during the Screening period in case the first measurement is missing/unreadable/invalid.

4. K^+ ≤4.8 mmol/L at Screening (local assessment)
    - Note: One re-assessment is allowed for potassium during the Screening period
5. Participants with a clinical diagnosis of CKD and fulfilling both the criteria (central assessment):
    - eGFR ≥25 and <90 mL/min/1.73 m^2 using CKD-EPI 2009 formula (Section 10.2) at the Screening visit
    - UACR ≥200 mg/g (22.6 mg/mmol) to <5000 mg/g (565 mg/mmol) at the Screening visit (geometric mean of the 3 measurements)
      and documentation of elevated albuminuria or proteinuria* in the participant's medical records at least 3 months prior to Screening.
        * 1 quantitative or semiquantitative record documented in the participant's medical records

      If no documentation of elevated albuminuria or proteinuria is available in the medical history, the Pre-screening UACR assessment could be used instead (see Section 4.1).

    Note: One reassessment of eGFR and/or UACR is allowed during the Screening period.
6. Participants on a stable (preferably without any change in the dosage for at least 4 weeks prior to the Screening visit) ACEI or ARB treatment.

Sex and Contraceptive/Barrier Requirements

7. Male or female

Male participants: there are no contraceptive measures required for the study.

Contraceptive use by **women** should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Female participants:

- A female participant is eligible to participate if she is not pregnant or breastfeeding, and one of the following conditions applies:
    - Is a woman of nonchildbearing potential (WONCBP) as defined in Appendix 4 (Section 10.4).

      OR
    - Is a WOCBP and using an acceptable contraceptive method as described in Appendix 4 (Section 10.4) during the study intervention period (at a minimum until after the last dose of study intervention). The investigator should evaluate the potential for contraceptive method failure (e.g., noncompliance, recently initiated) in relationship to the first dose of study intervention.
- A WOCBP must have a negative highly sensitive pregnancy test (urine or serum/plasma as required by local regulations) within 4 days before the first dose of study intervention, see Section 8.3.5.
    - If a urine test cannot be confirmed as negative (e.g. an ambiguous result), a serum/plasma pregnancy test is required. In such cases, the participant must be excluded from participation if the serum/plasma pregnancy result is positive.

- Additional requirements for pregnancy testing during and after study intervention are located in Section 8.3.5.
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

8. Capable of giving signed informed consent as described in Section 10.1.3 which includes compliance with the requirements and restrictions listed in the informed consent form and in this protocol. Participants not capable of giving signed informed consent will not be enrolled into this clinical trial.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Participant with T2D.
2. Participant with other known causes of CKD than T1D.
3. Participant with kidney transplantation.
4. Known hypersensitivity to the study intervention (active substance or excipients).
5. Participant with hepatic insufficiency classified as Child-Pugh C (Section 10.6)

   Note: Assessment of relevant laboratory parameters is only required if there is a clinical suspicion of hepatic insufficiency.
6. Participant with mean BP higher than 160/100 mmHg or mean systolic BP lower than 90 mmHg at the Screening visit (Section 8.3.2).
7. Participant hospitalized due to a CV event within 4 weeks prior to Screening visit (heart failure decompensation, acute coronary syndrome, stroke, transient ischemic attack, acute limb ischemia).
8. Participant with acute kidney injury requiring dialysis within 24 weeks prior to the Screening visit.
9. Symptomatic heart failure with reduced ejection fraction with class 1A indication for MRAs.
10. Participant with Addison's disease.
11. Any other history, condition, therapy or uncontrolled intercurrent illness which would make the participant unsuitable for this study and will not allow participation for the full planned study period (e.g., active malignancy or other condition limiting life expectancy to less than 12 months).

Prior/Concomitant Therapy

12. Concomitant dual therapy with both an ACEI and an ARB which cannot be discontinued for the purpose of the study at least 8 weeks prior to the Screening visit.

13. Participants with current or previous (within 8 weeks prior to the Screening visit) treatment with a SGLT-2/-1 inhibitor or GLP1 receptor agonist.
14. Participants concomitantly treated with strong CYP3A4 inhibitors not stopped at least 7 days prior to randomization.
15. Participants concomitantly treated with moderate/strong CYP3A4 inducers not stopped at least 7 days prior to randomization.
16. Concomitant therapy with eplerenone, spironolactone, canrenone, esaxerenone, any renin inhibitor, sacubitril/valsartan combination, or potassium-sparing diuretic which cannot be discontinued at least 8 weeks prior to the Screening visit.

Prior/Concurrent Clinical Study Experience

17. Previous assignment to study intervention during this study
18. Simultaneous participation in another interventional clinical study (e.g. Phase 1 to 3 clinical studies) or treatment with any investigational medicinal product within 8 weeks prior to randomization.

Other Exclusion Criteria

19. Participants known for lack of compliance with clinic visits or prescribed medication.
20. Known current alcohol and / or illicit drug abuse that may interfere with the participant's safety and / or compliance at the discretion of the investigator.
21. Close affiliation with the investigational site; e.g. a close relative of the investigator, dependent person (e.g. employee or student of the investigational site).

5.3 Lifestyle Considerations

Meals and Dietary Restrictions

Grapefruit or grapefruit juice should not be consumed during the study intervention period.

5.4 Screen Failures and Re-screening

A screen failure occurs when a participant has consented to participate in the clinical study but is not subsequently assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, and SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened once. The following conditions are pre-requisites of re-screening:

- A minimum of 1 month between the initial Screening visit and re-screening.
- Before re-screening, new documented informed consent must be obtained
- Allocation of a new participant identification number

- All screening assessments for the study must be repeated

Sites will also have the option of a Pre-screening visit to examine UACR (see Section 4.1). This UACR value is not valid to determine eligibility, and is only to be used to assess whether the participant may progress to a formal screening visit. Pre-screening failures will not be considered as part of the study population and should not proceed to Screening.

5.5 Criteria for Temporarily Delaying Screening / Randomization / Study Intervention Administration

The following conditions may allow a participant to be randomized or started on study intervention once the condition has resolved and the participant is otherwise eligible:

- Current febrile illness (body temperature ≥38.0ºC [100.4º F]) or other acute illness within 48 hours before study intervention administration.
- Menstruation precluding urine collection scheduled for Visit 2
- Pre-screening showing albuminuria, if not documented previously in the participant's health records. In this case, the Screening visit may be delayed by at least 3 months for inclusion criterion number 5 to be fulfilled.
- The screening window can be extended if the central laboratory results are still pending. As soon as central laboratory results are available, they should be reviewed by the investigator to confirm participant eligibility, even if he/she is out of screening window. All screening procedures/assessments must be completed before randomization occurs.

6. Study Interventions and Concomitant Therapy

Study interventions are all pre-specified, investigational and non-investigational medicinal products, medical devices and other interventions (e.g., surgical and behavioral) intended to be administered to the study participants during the study conduct.

6.1 Study Interventions Administered

Finerenone 10 mg and 20 mg tablets and matching placebo will be supplied by the Sponsor (Table 6–1). The finerenone immediate-release 10 mg and 20 mg dose strengths are the marketed formulation.

Table 6–1:Study intervention

Arm Name	Finerenone	Placebo
Intervention Name	Finerenone	Placebo
Intervention Description	Finerenone 10 mg film-coated tablets given OD orally. Finerenone 20 mg film-coated tablets given OD orally.	Appearance is identical to finerenone tablets
Type	Drug	Drug
Dose Formulation	Tablet	Tablet
Unit Dose Strength(s)	10 mg and 20 mg	Not applicable
Dosage Level(s)	One tablet OD, 10 mg once daily or 20 mg once daily	One tablet OD
Route of Administration	Oral	Oral
Use	Experimental	Placebo
Packaging and Labeling	Study intervention will be provided in bottles. Each bottle will be labeled as required per country requirement	Study intervention will be provided in bottles. Each bottle will be labeled as required per country requirement
Current/Former Name(s) or Alias(es)	BAY-94-8862, Finerenone, Kerendia, Firialta	Not applicable

OD = once daily

Study intervention will be dispensed starting from Visit 2 (randomization) as summarized in the SoA (Section 1.3). Returned study intervention should not be re-dispensed to the participants.

As shown in Table 6–2, the starting dose of finerenone will depend on the eGFR value at the Screening visit.

Dosage of study intervention

At randomization, participants with an eGFR between 25 to <60 mL/min/1.73 m² at the Screening Visit (central laboratory results) will be assigned to the lower dose of finerenone (10 mg) or placebo in addition to SoC, whilst participants with an eGFR ≥60 mL/min/1.73 m² will be assigned to the higher dose of finerenone (20 mg) or placebo in addition to SoC.

The investigator is encouraged to up-titrate the dose of study intervention at any time once the participant has been on a stable dose for 4 weeks (±7 days) (e.g. from Month 1 onwards for participant starting study intervention on the lower dose) either at a regular visit or a 4-week Safety visit (Table 6–2). For more details on dose modification refer to Section 6.6.

Table 6–2: Dosage of study intervention for administration

eGFR value at the Screening Visit, based on central laboratory results:	**25 to < 60 mL/min/1.73m²**		**≥ 60 mL/min/1.73m²**	
Participant randomized to arm: Receives	**Finerenone** 10 mg finerenone OD + SoC	**Placebo** Placebo OD + SoC	**Finerenone** 20 mg finerenone OD + SoC	**Placebo** Placebo OD + SoC
Study intervention intake	One tablet of study intervention once daily, preferably in the morning at approximately the same time each day. The study intervention may be taken with a glass of water, with or without food. Note: Study intervention will be administered at home, except on Day 1 when the tablet will be taken at the study site.			
Missed intake	• If >8 hours before the next scheduled dose, the participant should take one tablet of study intervention as soon as possible. • If ≤8 hours of the next scheduled dose, the participant should wait and take the next tablet of study intervention at the usual time.			
Up-titration of dose Allowed from Visit 3 (Month 1) onwards provided that: • Potassium is ≤4.8 mmol/L [a] • eGFR decrease is less than 30% below the value measured at the last scheduled visit [a] • Must be documented in eCRF	20 mg finerenone OD, maintain SoC	Sham-titrate, maintain SoC	Not applicable	Not applicable
Down-titration of dose • Only for safety reasons • Allowed any time during the study (e.g. between scheduled visits) • Must be documented in eCRF	• If at higher dose of study intervention, down-titrate to lower dose of study intervention, maintain SoC • If at lower dose of study intervention, interrupt study intervention, maintain SoC			

eCRF = electronic case report form, eGFR = estimated glomerular filtration rate, OD = once daily, SoC = standard of care

a Potassium and eGFR according to local laboratory values

Up- and down-titration or interruption of study intervention

The dose level of study intervention should be adjusted (up-titrated, down-titrated or interrupted) on the basis of potassium and eGFR levels obtained from the local laboratory as summarized in Table 6–2 and Table 6–3.

The investigator is encouraged to up-titrate the dose of study intervention at any time once the participant has been on a stable dose for 4 weeks (±7 days) (e.g. from Month 1 onwards for participant starting study intervention on the lower dose of 10 mg OD) either at a regular visit or a 4-week Safety visit.

Participants who started with or were up-titrated to the target dose (20 mg OD) of the study intervention but who do not tolerate this dose may be down-titrated at any point during the study, including between-scheduled visits if required for safety reasons. These participants may be up-titrated again based on the rules provided in Table 6–2. If the participant is already at the lower dose, the study intervention can be interrupted at the investigator's discretion

(refer to Section 6.6 for guidance). If the study intervention is interrupted for more than 7 days, the study intervention should be re-started at the lower dose (10 mg OD).

Subsequent to an up-titration or re-start of study intervention after interruption of study intervention intake for more than 7 days, the investigator should perform a 4-week Safety visit (±7 days) after titration or restart, to monitor potassium levels and renal function via eGFR (see the SoA in Section 1.3). If a regular study visit will be scheduled to take place 4 weeks (±7 days) after up-titration, the monitoring of potassium and renal function is assured and no 4-week Safety visit has to be performed in addition. With down-titrations, an unscheduled Safety visit may be performed at the investigator's discretion.

At any point during study intervention treatment, if blood potassium is found to be elevated, study intervention treatment should be adjusted as described in Section 6.6.

Both up- and down-titrations will be at the investigator's discretion and will depend on the general clinical condition of the individual participant. The investigator should attempt to reach the maximum (target) dose of study intervention as long as safety is not compromised and the guidance for the up- and down titration is followed.

In cases where the investigator estimates that the participant is at higher risk of developing hyperkalemia (e.g. previous hyperkalemia, high serum potassium and lower eGFR), additional potassium measurements may be performed at any time as part of unscheduled visits at the investigator's discretion.

All titrations, including the reasons for down-titration or for not dispensing the 20 mg dose, must be documented in the eCRF.

6.1.1 Medical Devices

Not applicable.

6.2 Preparation, Handling, Storage, and Accountability

1. The investigator or designee must confirm study interventions have been received and, if a temperature data logger has been included, appropriate temperature conditions have been maintained during transit. Any discrepancies are to be reported and resolved before use of the study interventions.
2. Only participants randomized in the study may receive study intervention and only authorized site staff may supply, prepare or administer study intervention.
3. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
4. The investigator or head of institution (where applicable), or authorized site staff is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records). Drug returns, reconciliation and destruction/return information will be captured in an Interactive Response Technology (IRT).
5. Further guidance and information for the final disposition of unused study interventions are provided in the investigator site file.

6.3 Assignment to Study Intervention

All participants will be centrally assigned in a 1:1 ratio to randomized study intervention using an Interactive Response Technology (IRT). To accomplish random assignments, computer-generated randomization lists specified by the sponsor's responsible statistician will be prepared by the study sponsor or delegate. The randomization lists are provided to an IRT vendor. Before the study is initiated, the log in information and directions for the IRT will be provided to each site.

6.4 Blinding

As this is a double-blind study, investigators, participants and study personnel will remain blinded to each participant's assigned study intervention throughout the course of the study. To maintain the blind, study interventions will be packaged in bottles labeled with a unique number which will be pre-printed on each bottle.

The IRT system, and investigational medicinal product labels are designed to maintain the treatment blind to the investigator and sponsor personnel, however the dose assignments (10 mg or 20 mg tablets) are not blinded. The IRT system will need to assign (a) new bottle(s) of study intervention at every dose modification (up- or down-titration).

Sponsor personnel responsible for bioanalytics will be unblinded and will have access to the randomization list.

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the responsibility for determining if unblinding of a participant's intervention assignment is warranted. If the investigator is unavailable, and a treating physician not associated with the study requests emergency unblinding, the emergency unblinding requests are forwarded to the emergency medical advice 24 hours/7 day service. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the decision depends solely on each individual case and the investigator´s own judgement. The investigator may contact the sponsor prior to unblinding should they wish; this discussion should not delay the final decision for unblinding. If a participant's intervention assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form, as applicable.

Sponsor pharmacovigilance staff may unblind the intervention assignment for any participant with a SUSAR. If the SUSAR requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's intervention assignment, may be sent to investigators in accordance with local regulations and/or sponsor policy.

6.5 Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study

intervention and study participant identification will be confirmed against the dispensing information provided by the IRT system, at the time of dosing by a member of the study site staff other than the person administering the study intervention.

When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by direct questioning and counting of returned tablets during the site visits and documented in the source documents and relevant form.

An adequate record of receipt, distribution, and return/destruction of all study intervention must be captured on the dispensing log and in the IRT. Intervention start and stop dates, including dates for intervention delays and/or dose adjustments will also be recorded.

Overall compliance with study intervention intake should be between 80% and 120% of the scheduled dose at the end of study intervention treatment.

Deviation(s) from the prescribed dosage regimen should be recorded. Study intervention tablets not returned will be considered to have been taken unless otherwise specified. At the end of the study, any remaining drugs will be collected and returned to the sponsor, destruction depot or destroyed at the site. Any discrepancies between the returned and expected returned study interventions should be explained.

6.6 Dose Modification

The dose of study intervention should be adjusted (up- or down-titration) on the basis of potassium and eGFR levels obtained from the local laboratory (see Section 6.1).

Monitoring of blood potassium and dose adjustment

Hyperkalemia is a frequent event in participants with CKD with decreasing eGFR, and the risk identified for treatment with finerenone (see Section 2.3.1).

Since the value of potassium in the local sample is usually less affected by sample handling and extended transportation time, local samples will be taken for safety purposes and dose adjustments.

Re-checking of potassium values must be done at the latest within 72 hours of the investigator being aware of results that need confirmation (>5.5 mmol/L). The investigators can perform a re-test at any time if they consider it necessary to confirm the potassium concentration of the local or the central sample.

Adjustment of dose after start of study intervention intake based on blood sample potassium levels is provided in Table 6–3.

Table 6–3: Potassium from blood sample: guidance for dose adjustment at Visit 3 (Month 1) and subsequent visits

Blood potassium (mmol/L)	Action
First sample:	
≤4.8	If on lower dose of study intervention (10 mg), up-titrate to higher dose (20 mg). If on higher dose of study intervention (20 mg), continue on the same dose.
4.9 to 5.5	Continue on the same dose.
>5.5	Withhold study intervention and re-check potassium within 72 hours.
Second and subsequent samples:	
≤5.0	Re-start study intervention at the lower dose (10 mg).
>5.0	Continue to withhold study intervention; continue to monitor potassium and restart study intervention at the lower dose (10 mg) only if potassium is ≤5.0

The following aspects have also to be taken into consideration:

- Potassium should be measured 4 weeks (±7 days) after re-starting treatment if treatment was interrupted for >7 days and 4 weeks (±7 days) after up-titration.
- If central laboratory results for potassium differ from local laboratory results to such an extent that the investigator is uncomfortable with the dose adjustment guidance shown in Table 6–3, blood sampling may be repeated at the investigator's discretion.
- If the participant is already on the lower dose of study intervention but hyperkalemia recurs soon after a previous event of hyperkalemia with interruption of study intervention, and there is no explanation for the recurring hyperkalemia event other than intake of study intervention, permanent discontinuation of study intervention is recommended.
- If blood potassium is >6.5 mmol/L, an ECG should be obtained.

6.7 Continued Access to Study Intervention after the End of the Study

No continued access to the study intervention is planned following the end of the study.

6.8 Treatment of Overdose

In this trial, an overdose is defined as any occasion when the participant has taken (accidentally or intentionally) any dose higher than the maximal target dose prescribed in the protocol.

The most likely manifestation of overdose is anticipated to be hyperkalemia. If hyperkalemia develops, standard treatment should be initiated. Finerenone is unlikely to be efficiently removed by hemodialysis given its fraction bound to plasma proteins of about 90%.

In the event of an overdose, the investigator should:

- Contact the Medical Monitor.

- Evaluate the participant to determine, in consultation with the medical monitor, if possible, whether study intervention should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities as clinically indicated (at least 1 day).
- Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent (see Section 10.3.1).

6.9 Prior and Concomitant Therapy

All treatment that the investigator considers necessary for the participant's welfare may be administered at the discretion of the investigator in keeping with the standards of medical care.

Any relevant medication of interest (including over the counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) that the participant is receiving within 8 weeks prior to screening, or receives during the study (including any vaccine) must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.9.1 Standard of Care (SoC) Medications

To be eligible, the participant needs to be on stable daily dose (preferably without any change in the dosage for at least 4 weeks prior to the Screening visit) of ACEI or ARB.

The stable dose of ACEI or ARB should ideally be unchanged throughout the course of the study.

The dosage of SoC therapies should not be reduced to solely facilitate maintenance of study intervention.

6.9.2 Potassium Supplements and Lowering Agents

Potassium supplementation can be prescribed during the course of the study. To assure the potassium value is within the normal range, investigators are advised to monitor potassium carefully at each visit and to adapt the dose of potassium supplementation accordingly.

Potassium-lowering agents (e.g. sodium polystyrene sulfonate, calcium polystyrene sulfonate) are allowed to be started during treatment with study intervention.

Any use of potassium supplementation and potassium-lowering agents must be documented in the eCRF.

6.9.3 Low Dose Steroids

Careful consideration should be made for immunosuppressive therapy with high dose steroids. Topical, inhaled or low dose steroids (dose equivalent of daily 5-10 mg of prednisolone) are allowed if used for non-renal indication.

6.9.4 Prohibited Concomitant Medication

The following therapies are NOT permitted:

- Concomitant therapy with both an ACEI and an ARB
- Concomitant treatment with a SGLT-2/-1 inhibitor or GLP1 receptor agonist
- Concomitant treatment with strong CYP3A4 inhibitors
- Concomitant treatment with moderate/strong CYP3A4 inducers
- Concomitant therapy with eplerenone, spironolactone, canrenone, esaxerenone, any renin inhibitor, sacubitril/valsartan combination, or potassium-sparing diuretic.

An updated list of the most common medication regarded as strong CYP3A4 inhibitors or moderate or strong CYP3A4 inducers will be provided separately.

Caution: Increases in finerenone exposure in combination with moderate CYP3A4 inhibitors cannot be excluded.
Examples of moderate CYP3A4 inhibitors are: amiodarone, aprepitant, bicalutamide, chloramphenicol, imatinib, mifepristone, norfloxacine, tacrolimus, verapamil, lapatinib, dasatinib, and nilotinib.

Additional monitoring of serum potassium during initiation or dosage adjustment of moderate or weak CYP3A4 inhibitors should be considered, particularly in participants with moderate hepatic impairment (Child-Pugh B).

Caution should also be exercised with non-steroidal anti-inflammatory agents or trimethoprim or trimethoprim / sulfamethoxazole. Finerenone treatment may be interrupted before trimethoprim or trimethoprim / sulfamethoxazole is started.

6.9.5 Rescue Medicine

Not applicable.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

Reasons for discontinuation of study intervention and participant discontinuation of the study are summarized in Table 7–1.

Discontinuation of specific sites or of the study as a whole are detailed in Appendix 1.

Table 7–1: Discontinuation of study intervention and participant discontinuation

Study intervention discontinuation	Participant discontinuation
Must be permanently discontinued	
Pregnancy of the study participant	At their own request. At any time during the study and without giving reasons, a participant may decline to participate further. The participant will not suffer any disadvantage as a result
The investigator is of the opinion that continuation of treatment with study intervention is harmful to the participant's well-being	
The randomization code is broken by the investigator, or other responsible person, when knowledge of the participant's treatment is required	
Any investigational drug other than the study intervention is used.	
May be permanently discontinued	
Any suspected drug-related AE or SAE	If, in the investigator's opinion, continuation of the study would be harmful to the participant's well-being
If any exclusion criterion applies during treatment	At the specific request of the sponsor and in liaison with the investigator.
If a significant violation of the protocol occurs, as defined by the sponsor and the coordinating investigator.	

AE = Adverse event, SAE = Serious adverse event

7.1 Discontinuation of Study Intervention

7.1.1 Permanent Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention (see Table 7–1). Study intervention discontinuation for any reason does not constitute withdrawal from the study and should not lead to the participant being withdrawn from the study. On the contrary, participants permanently discontinuing study intervention should attend the PD visit and the FU visit and then continue with all remaining protocol specified study visits up to the Month 6 visit, although study intervention is no longer administered. They will be encouraged to perform all assessments as stipulated in the SoA (Section 1.3).

Ad hoc additional telephone contacts may also be requested (e.g. close to the end of the study). These may be made to the participant themselves or to other contact as provided by the participant, where permissible per local regulations, e.g. a next of kin, primary physician (or local equivalent).

7.1.2 Temporary Discontinuation of Study Intervention

Interruption of study intervention is permitted at any time during the study for safety reasons. Upon temporary interruption of the study intervention due to hyperkalemia, eGFR decrease, (S)AE, intolerability or any other reason, intake should be resumed as soon as medically acceptable at the discretion of the investigator. There is no defined maximum time limit for temporary interruption. In all cases, the reason for study intervention interruption must be recorded in the eCRF and the participant's medical records (see Table 6–2 and Section 6.6 for guidance).

7.2 Participant Discontinuation/Withdrawal from the Study

- The definition of withdrawal of consent is deemed to be when the participant does not agree to any kind of direct/indirect follow up and actively refuses any further collection of data. Therefore this should only occur in rare and exceptional circumstances. Withdrawal from study intervention, and withdrawal from the study visits do not constitute withdrawal of consent.
- A participant may withdraw from the study at any time at the participant's own request, for any reason (or without providing any reason).
- A participant may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons.
- At the time of discontinuing from the study, if possible, a PD visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued from the study intervention and the study at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

7.3 Lost to Follow Up

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, telephone calls, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

8. Study Assessments and Procedures

8.1 Administrative and General Procedures

- Study procedures and their timing are summarized in the SoA (Section 1.3; refer to Section 4.1 for details to screening, study intervention and follow-up). Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA (Section 1.3), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., laboratory) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA (Section 1.3).
- In the event of a significant study-continuity issue (e.g., caused by a pandemic), alternate strategies for participant visits, assessments, medication distribution and monitoring may be implemented by the sponsor or the investigator, as per local health authority/ethics requirements
- Central laboratory results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

8.2 Efficacy Assessment: UACR

At the timepoints indicated in the SoA (Section 1.3) UACR will be assessed by the Central laboratory (Section 10.2). At each of those visits (except the optional pre-screening), the geometric mean of 3 samples will be calculated.

For all visits (except the optional pre-screening) three first morning urine samples will be collected at the participant's home on the 2 consecutive days before each scheduled visit, and on the morning of the respective visit. Detailed Urine Collection Instructions are available and should be provided to the participants.

At screening, collection of 3 morning void samples is also allowed on 3 consecutive days after the Screening visit. If one of the 3 UACR measurements is invalid but the other 2 are

valid, these values can be used to assess participant's eligibility for this study. If only 1 sample is achieved, collection of another 3 consecutive samples for reassessment is needed, which is allowed once at Screening.

Urine should not be collected while a female participant is menstruating. In this case, the collection should be delayed until menstruation has stopped. The delay can be handled by either postponing the visit within the allowed visit window and/or delay the collection of urine after the visit within up to two weeks if taking study intervention at the same dose level, and within one week after a change of the dose level.

8.2.1 Recording of Intercurrent Event

ESRD as the most important ICE (apart from death), is defined as follows:

- Occurrence of ESRD
    - Initiation of chronic dialysis (hemodialysis or peritoneal dialysis) for at least 30 days
    - Renal transplantation

Respective events will be recorded in the eCRF.

8.3 Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (Section 1.3).

8.3.1 Physical Examinations

A complete physical examination will include, at a minimum, assessments of the cardiovascular and respiratory systems. Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.2 Vital Signs

- Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 heart rate and 3 blood pressure measurements (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute).
- Blood pressure and pulse measurements will be assessed in sitting position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).

Height will be measured and recorded at the Screening Visit only.

Body weight will be measured and recorded at the Screening Visit and again at the Month 6 Visit.

8.3.3 Electrocardiograms

- A 12-lead ECG will be obtained in a supine position, using an ECG machine, with a preferred speed of 50 mm/s, that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals at Randomization (Day 1). Evaluation for safety will be signed by an investigator.
- If there is any clinical indication, unscheduled 12-lead ECGs can be performed at any point during the study.
  An additional 12-lead ECG should be obtained if (local) blood potassium is >6.5 mmol/L (Section 6.6).
- The interpretation of the tracing must be made locally by a qualified physician.
- Clinically significant abnormalities that fulfill the AE reporting criteria described in Section 8.4 should be reported as AEs as appropriate (e.g. new onset atrial fibrillation) when not already reported in the medical history or in one of the previous recordings and in case of worsening of previous findings.
- The date of the recording must be documented on the ECG section of the eCRF. Each ECG, paper or electronic tracing should be labeled with the study number, participant number, and date and kept in the source documents at the study site.

8.3.4 Clinical Safety Laboratory Assessments

- See Section 10.2 for the list of clinical laboratory tests to be performed and the SoA in Section 1.3 for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically significant abnormality that fulfills the AE reporting criteria described in Section 8.4 as an AE. The laboratory reports must be retained with the source documents.
- Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 3 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or the medical monitor.

  If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.

  All protocol-required laboratory tests, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA.

  If laboratory values from non-protocol specified laboratory tests performed at the institution’s local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded.

8.3.5 Pregnancy Testing

For WOCBP, a pregnancy test (urine, serum or plasma as required by local regulations) will be conducted at Screening. A repeat test at Day 1 (before intake of study intervention) is required, unless ≤4 days lie between Screening and first intake of study intervention (see SoA in Section 1.3).

Further pregnancy tests will be performed throughout the course of the study, if required by local regulations.

8.4 Adverse Events (AEs), Serious Adverse Events (SAEs) and Other Safety Reporting

The definitions of adverse events (AEs) and serious adverse events (SAEs) can be found in Section 10.3.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs that are serious, AESI, and non-serious AEs considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention (Table 7–1, see targeted AE reporting Section 8.4.1). This includes events reported by the participant.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

8.4.1 Time Period and Frequency for Collecting AE and SAE Information

(S)AEs will be collected from the start of study intervention until the last visit (Follow-up visit for participants who completed study intervention or Month 6 Visit for the participants who prematurely discontinued the study intervention, see Section 4.1) at the time points specified in the SoA (Section 1.3). (S)AEs which are related to protocol-required study procedures (e.g., (S)AE related to invasive study procedures) will be recorded as (S)AEs from the signing of the ICF.

Any medical occurrences/conditions that begin in the period between signing ICF and the start of study intervention, and which are not related to a protocol-required study procedure, will be recorded on the Medical History/Current Medical Conditions, not as AEs.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours of learning of the event, as indicated in Section 10.3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

With the exception of hyperkalemia, which will be collected as an AESI (see Section 8.4.6), non-serious AEs are not mandatory to be collected in the eCRF (targeted AE reporting). Instead, only the following non-serious AEs will be recorded in the eCRF:

- Non-serious AEs leading to permanent discontinuation of study intervention,
- Non-serious AEs considered related to study intervention by the investigator,
- Non-serious AEs considered related to protocol required procedures,

- any other non-serious AEs if deemed relevant by the investigator.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.4.2 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.4.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, AESI, and non-serious AEs as described above (Section 8.4.1) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.3.

8.4.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review boards (IRBs)/independent ethics committees (IECs), and investigators.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.
- Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

8.4.5 Pregnancy

- Details of all pregnancies in female participants will be collected after the start of study intervention and until 30 days after the last dose of study intervention.
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the female participant pregnancy.

- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs, and will be reported as such.
- The female participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the female participant and the neonate and the information will be forwarded to the sponsor.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.4.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention.

For contraceptive guidance and collection of pregnancy information see Section 10.4.

8.4.6 Adverse Events of Special Interest

Hyperkalemia will be an AESI in this study and collected in the eCRF. Only hyperkalemia that qualifies as an SAE will be reported to PV within 24 hours of awareness.

8.5 Pharmacokinetics

No dedicated PK sampling is planned.

8.6 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7 Genetics

Genetic as well as non-genetic analyses may be part of the biomarker investigations in this study if approved by local IECs / IRBs and competent authorities. Genetic analyses address e.g. 1) altered drug metabolism (pharmacogenetic analysis) or 2) factors predisposing to human diseases. Pharmacogenetic analyses relate to gene variants such as single nucleotide polymorphisms of drug transporters and/or drug metabolizing enzymes including enzymes of the cytochrome P450 system, the Solute Carrier Family or uridine 5′-diphosphate-glucuronosyltransferase. Different variants may predispose to altered metabolization of drugs and may result in differences in drug exposure. Specific genetic variants may arise during the clinical program.

Optional whole genome sequencing will be offered to all participants. See Section 10.5 for details.

Details on sample handling will be provided separately.

8.8 Biomarkers

In this study, genetic (see Section 8.7) as well as non-genetic biomarkers may be investigated. Biomarkers may be evaluated in samples collected before, during or after treatment to determine the impact of the study intervention. They may fall into the following categories:

- Biomarkers which are proximal to the target or otherwise related to the mode-of-action of the study intervention (pharmacodynamic biomarkers).
- Functional markers of the cardiovascular system, such as vasoactive agents (aldosterone etc.), NT-proBNP/BNP.
- Exploratory biomarkers - measured e.g. by omics techniques - to identify or further investigate exploratory pharmacodynamic biomarkers. This could comprise e.g. targeted or untargeted metabolomics, proteomics (e.g. OLINK etc.).
- Further biomarkers related to the mode of action or the safety of study intervention and similar drugs may be examined. The same applies to further biomarkers deemed relevant to renal and (cardio)vascular diseases and associated health problems. These investigations may include e.g. diagnostic, safety, pharmacodynamic, monitoring, or potentially predictive biomarkers.

Timing of sample collection for biomarker samples:

The planned time points of sample collection are provided in the SoA (Section 1.3). If deemed necessary, the sampling time points or frequency according to the SoA may be adjusted, e.g. in case morning void urine samples would only be collected after the Screening visit.

Specimen Types:

The following sample types will be collected for biomarker analysis: plasma, serum, whole blood, urine. Safety laboratory samples (leftovers) may be used for biomarker investigations if deemed necessary during the study conduct. The exact specimen type for a particular biomarker (e.g. serum or plasma) will be provided in separate documents (e.g. sample handling sheets or laboratory manual).

Sample handling and storage:

Details on the collection, processing, shipment and storage of samples will also be provided in separate documents (e.g. sample handling sheets or laboratory manual). Samples may be stored for a maximum of 15 years (or according to local regulations) following the end of the study at a facility selected by the Sponsor to enable further analyses.

Reporting:

Biomarker investigations may be reported separately (e.g. in a biomarker evaluation report) or within the Clinical Study Report. If biomarker analyses are conducted during the study and if described in the SAP, results may also be reported in the main Clinical Study Report of this study.

8.9 Immunogenicity Assessments

Not applicable.

8.10 Health Economics

Health economics parameters are not evaluated in this study.

9. Statistical Considerations

This section is a summary of the planned statistical analyses including the primary efficacy estimand. The statistical analysis plan will be finalized at the latest prior to the blind review meeting and it will include a more technical and detailed description of the statistical analyses described in this section. The analysis and reporting will be done on all data from all participants at the time the study ends.

9.1 Statistical Hypothesis

The primary hypotheses to be tested for the primary estimand are provided below:

$$H_0: \mu_1 / \mu_2 = 1$$

$$H_1: \mu_1 / \mu_2 \neq 1$$

or equivalently

$$H_0: \log(\mu_1) - \log(\mu_2) = 0$$

$$H_1: \log(\mu_1) - \log(\mu_2) \neq 0$$

Where μ_1 and μ_2 are the mean ratios to baseline of UACR over 6 months for finerenone and placebo, respectively. Here, μ_1 is defined as the geometric mean of the mean ratios to baseline of UACR at Month 3 (Visit 4) and Month 6 (Visit 5) in the finerenone group, and μ_2 is defined analogously for the placebo group. The null hypothesis (H_0) is defined as no difference in change in UACR between the treatment arms over 6 months. The alternative hypothesis (H_1) states that the two groups change in UACR over 6 months are different, where a ratio μ_1/μ_2 below 1 indicates superiority of finerenone over placebo.

The primary estimand will be tested under a confirmatory testing procedure. If the primary efficacy endpoint achieves the two-sided significance level of 0.05, the corresponding null hypothesis can be rejected.

9.2 Analysis Sets

For the purposes of analysis, the following analysis sets are defined:

Enrolled:	All participants who sign the Informed Consent Form.
Full analysis set (FAS):	All randomized participants.

Safety analysis set (SAF): All randomized participants who have taken at least one dose of the study intervention.

All participants will be analyzed according to the planned treatment in the FAS (i.e. as randomized). All participants will be analyzed according to the actual treatment in the SAF.

The FAS is used to analyze endpoints/estimands related to the efficacy objectives and the SAF is used to analyze the endpoints and assessments related to safety.

9.3 Statistical Analyses

9.3.1 General Considerations

Statistical analysis will be performed using SAS; the version used will be specified in the SAP.

A lognormal distribution for UACR is assumed, therefore the log-transformed values of UACR will be analyzed. Geometric statistics and ratios to baseline will be presented for UACR instead of arithmetic statistics with changes from baseline.

For all other continuous variables, a normal distribution is assumed. The distributional assumptions will be investigated. If necessary, nonparametric methods or transformation of the data will be considered.

All variables will be analyzed by treatment arm using descriptive statistical methods. The number of data available, mean, SD, minimum, median, and maximum, will be calculated for continuous data. The geometric mean and SD will be provided instead of the arithmetic mean and SD for the variables where lognormal distributions are assumed. Frequency tables will be generated for categorical data.

Baseline values will be defined as the central laboratory value from randomization (Day 1). If the last observation available prior to randomization is the measurement from the Screening Visit, this would be used as the baseline value. Otherwise baseline values will be missing. If more than one measurement was planned for a scheduled time point, for example blood pressure measurements and heart rate, the mean value of the last set of measurements per time point prior to randomization will be used for the calculation of the baseline value.

Only centrally analyzed samples will be considered for statistical analysis, unless otherwise specified.

In the event of repeated measurements for screening (Visit 1) and baseline (Visit 2), the closest measurement prior to randomization will be used for analysis instead of the scheduled measurements. At all visits post-randomization and, unless stated otherwise, only the values at scheduled measurements will be used for analysis.

9.3.1.1 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized using descriptive statistics by treatment arm and all participants for FAS and SAF. Age for each participant will be defined as the number of years between informed consent date and birth date. For summarizing race, if multiple races are recorded in the database, then 'multiple race' will be used in the summary

table. The study sample sizes will be summarized by the trial unit (site) for enrolled participants. All participants with signed ICF will be included in the enrolled participants.

9.3.1.2 Incomplete or Missing Values

It is important to minimize the amount of missing data for the analysis of the primary estimand. Certain measures will be taken to guarantee the availability of all UACR values as possible (e.g. early site training on the importance of retention, option to use local laboratory samples in case central laboratory shipment is not possible).

Permanent study intervention discontinuation for any reason does not constitute withdrawal from the study and should not lead to the participant being withdrawn from the study (see Section 7.1.1), i.e. incomplete or missing values.

Data handling rules for incomplete data will be described in the specified section in the SAP if needed.

9.3.2 Primary Efficacy Endpoint/Estimand Analysis

9.3.2.1 Main Analytical Approach

The primary efficacy analysis will be performed on the primary efficacy estimand described in Table 3–1 and the study will be considered positive when this primary efficacy analysis is met.

A descriptive summary of UACR values over time will be presented by treatment group and visit. This will include descriptions of absolute and relative changes from baseline.

The analysis of UACR will be performed on the log-transformed UACR values, followed by a back transformation to the original scale. Accordingly, arithmetic means on the log scale correspond to geometric means on the original scale. The log-transformed ratio of UACR to baseline up to Month 6 (Visit 5) will be analyzed by a mixed model for repeated measures with the factors treatment group, visit, treatment by visit interaction, log-transformed baseline value as covariate and log-transformed baseline value by visit interaction to characterize the patient's baseline-specific response over time. Pairwise ratios between the finerenone and placebo group will be calculated for each visit and corresponding two-sided 95% confidence intervals and p-values will be computed. The primary estimand will be estimated by the geometric mean of the pairwise ratios between the finerenone and placebo group at Month 3 (Visit 4) and Month 6 (Visit 5) and the corresponding two-sided 95% confidence intervals and p-value will be provided. Covariance patterns within participants to adjust for the within subject variance will be estimated. For each treatment group a separate covariance pattern will be estimated based on an unstructured covariance. In case of convergency issues, an alternative covariance matrix will be used, with Toeplitz matrix as first choice alternative.

Missing data due to loss to follow-up will be imputed using data observed from participants who discontinue study intervention but remain in the study. It is assumed that participants who are lost to follow-up no longer have prolonged access to study intervention and therefore would follow a similar physical reaction to those participants who discontinue study intervention. Since participants who discontinue study intervention are encouraged to remain in the study, the data obtained from the "off-treatment" period will be used to impute the

values from the point where participants are lost to follow-up. Multiple imputation methodology will be applied to avoid underestimation of the standard error.

9.3.2.2 Intercurrent Event Strategy for the Primary Efficacy Estimand

To account for ICEs such as death and ESRD (for definition and recording refer to Section 8.2.1), a "worst case" approach will be applied, which represents a composite strategy. For participants experiencing the ICE, their subsequent UACR values will be set to a "worst case" value which reflects the seriousness of the event. The values will be drawn from the distribution of the largest change in UACR from baseline values observed during the trial (e.g. worst 10% of change in UACR from baseline values). Therefore the participants who do not have complete UACR measurements due to death or ESRD can be included in the primary analysis.

Treatment policy strategy relates to participants being followed up for the remainder of the study after discontinuing study intervention. Data from the visits after discontinuation of study intervention will be included in the analysis.

9.3.2.3 Supportive Analysis of the Primary Efficacy Estimand

Alternative estimands will be considered with different strategies for handling ICEs. For the ICEs of death and ESRD during the trial, a "while alive strategy" will be considered to assess the change in UACR while the participants are alive and have not experienced ESRD.

For the ICE permanent treatment discontinuation a "while-on-treatment strategy" will be considered to assess the change in UACR while the participants were taking study intervention.

Further details will be included in the SAP.

9.3.2.4 Sensitivity Analysis of the Primary Efficacy Estimand

To assess the robustness of the results for the primary efficacy estimand with respect to the impact of missing data, a 'tipping point analysis' will be performed utilizing multiple imputation methodology. Details of this analysis will be specified in the SAP.

9.3.3 Other Exploratory Efficacy Endpoints

The exploratory efficacy analyses will be performed on the other exploratory efficacy endpoints listed in Table 3–1.

Frequency tables will be generated for the number of participants with a relative decrease in UACR of ≥30% from baseline UACR.

At Month 6, the categorical variable of a relative UACR decrease of ≥30% from baseline will be analyzed for the presence or absence of the event using logistic regression including covariates for the treatment group and baseline UACR. The odds ratio between the finerenone and the placebo treatment group will be calculated, and corresponding two-sided 95% confidence interval and p-value will be presented.

These analyses will be repeated for the other exploratory efficacy endpoint of reduction ≥50% of UACR from baseline at Month 6.

Change in UACR from baseline to each visit will be analyzed as described for the primary analysis (Section 9.3.2.1).

Details will be specified in the SAP, as applicable.

9.3.4 Secondary Safety Endpoints and Other Safety Analysis

All safety analyses will be performed in the SAF.

The safety analysis encompasses the numbers of participants with TEAEs, TESAEs as well as hyperkalemia (AESI) that were pre-specified as secondary safety endpoints (Table 3–1). AEs that started or worsened after the first dose of study intervention up to 3 days after any temporary or permanent interruption of study intervention will be considered as TEAEs.

Furthermore, the following will be analyzed/assessed for safety:

- Based on AEs:
    - SAEs and AEs leading to discontinuation of treatment with study intervention
    - Number of participants with hospitalization for hyperkalemia
    - Number of participants discontinuing study intervention permanently due to hyperkalemia
    - Number of participants with hospitalization for worsening of renal function
    - Number of participants discontinuing study intervention permanently due to worsening of renal function
- Change in vital signs from baseline
- Based on (central) laboratory values:
    - Changes in laboratory values with a focus on eGFR and serum potassium
    - Number of participants with serum potassium >5.5 mmol/L
    - Number of participants with serum potassium >6.0 mmol/L

AE safety analysis

All safety variables collected in the study will be analyzed descriptively with appropriate summary measures.

The number, incidence and incidence rates per 1000 participants years of participants with (TE)AEs and (TE)SAEs will be summarized by treatment group and overall using MedDRA terms grouped by Primary System Organ Class and Preferred Term.

Tables and/or narratives of treatment-emergent deaths, serious and significant AEs, including early discontinuation due to AEs, will also be provided

TEAEs pertaining to hyperkalemia will be summarized by treatment group using frequency counts. For the number of participants with these events, the summary will be provided for all events and for all treatment-emergent events.

Vitals signs and laboratory analyses

Summary statistics including changes to baseline will be calculated by treatment group and visit for the central laboratory parameters including serum potassium. Descriptive summaries of the number of participants with an absolute value of serum potassium >5.5 mmol/L and >6.0 mmol/L will be displayed by treatment group and by visit.

Summary statistics including changes to baseline will be calculated for eGFR. The relative change will be displayed in addition to the absolute change from baseline.

It is assumed that after study intervention discontinuation the acute drop in eGFR observed at the start of study intervention intake will be negated by a rebound of similar magnitude after last intake of study intervention. A post treatment eGFR measurement will be taken for all participants 30 days after last dose of study intervention (at the Follow-up visit). An ANCOVA model will be fitted to summarize the treatment difference in the change from baseline value. The model will include treatment group as a factor and baseline eGFR as a covariate. Corresponding two-sided 95% confidence intervals and p-values will be produced.

Further details on safety analyses will be described in the SAP.

9.3.5 Other Analysis

Subgroup analyses

Exploratory subgroup analysis will be performed for the primary efficacy endpoint. The list of key subgroups and other subgroups analyzed is specified below. Analyses will include descriptive statistics, estimated ratios to baseline with 95% CIs.

If the result for a subgroup cannot be calculated due to a small sample size or number of events, then this subgroup will be dropped.

Key subgroups are:

- eGFR category at baseline (eGFR <45, 45 to <60, ≥60 mL/min/1.73 m²)
- UACR category at baseline (<300 mg/g, 300 to ≤1000 mg/g, >1000 mg/g)
- Region (North America, Europe, Asia)
- Race (white, black, Asian, other)
- Sex (male, female)
- Age group (<65, ≥65 years)
- Systolic BP (<130, ≥130 mm Hg)

9.4 Interim Analysis

No interim analysis is planned.

9.5 Sample Size Determination

UACR ratio will be analyzed assuming a lognormal distribution. Assumptions for the UACR ratios to baseline at 6 months are based on the FIDELITY UACR mixed model analysis restricted to patients with UACR ≥200 mg/g and eGFR between 25 and 90 mL/min/1.73 m^2. We shall assume the effect of placebo on UACR is non-existent, so for sample size

calculation we will assume a UACR ratio to baseline after 6 months of 1.00 for the placebo group.

In the FIDELITY restricted population, the UACR ratio to baseline after 4 months was 0.61 and 0.53 after 12 months in the Finerenone group. The value, using interpolation, at 6 months was estimated to be 0.59. As a conservative approach, we will assume the treatment ratio (finerenone/placebo) over 6 months to be 0.7 (i.e., the relative difference in UACR ratio to baseline between finerenone and placebo to be 30%). The standard deviation of the change from baseline of log-transformed UACR was calculated to range from 0.75 and 1.0 between month 4 and 12. Using linear interpolation, at Month 6 it was assumed to be approximately 0.8.

A sample size of 214 (107 per group) achieves 90% power at a two-sided significance level of 5%, to reject the null hypothesis of treatment ratio equal to 1 assuming the true treatment ratio of 0.7 and the standard deviation to be 0.8. To account for the potential loss of information in applying the “worst case” approach for the primary estimand, the sample size will be increased by 2.6% (the calculated cumulative incidence of death and kidney failure from the pool of FIDELIO-DKD and FIGARO-DKD) to ensure the desired power is achieved. Therefore, the sample size is increased to 220 participants (110 per group).

10. Supporting Documentation and Operational Considerations

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
    - Applicable ICH Good Clinical Practice (GCP) guidelines
    - Applicable laws and regulations (including EU regulation No. 536/2014)
- The protocol, protocol amendments, ICF, investigator's brochure, and other relevant documents (e.g., advertisements) must be submitted reviewed and approved in accordance with national legislation and undergo scientific and ethical assessment before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants. Any substantial modification of the protocol will be submitted to the competent authorities as substantial amendments for approval, in accordance with ICH Good Clinical Practice and national and international regulations.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following, as applicable:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
    - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
    - Providing oversight of the conduct of the study at the site and adherence to requirements of ICH guidelines, the IRB/IEC, and all other applicable local regulations.

10.1.2 Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3 Informed Consent Process

- The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the potential participants and answer all questions regarding the study.
- Potential participants must be informed that their participation is voluntary. They will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participants.
- Participants who are rescreened are required to sign a new ICF.
- In case any optional pre-screening visit is performed, a pre-screening consent form must be signed by the potential participants prior to any study specific procedure.

10.1.4 Recruitment Strategy

Detailed description of the recruitment strategy will be provided in country-specific documentation as required.

10.1.5 Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records, datasets or biological samples that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- Participants must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- Participants must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The contract between sponsor and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

10.1.6 Committees Structure

10.1.6.1 Steering Committee

The Steering Committee, which consists of external experts in the area of endocrinology and nephrology, will ensure the overarching integrity of the study, including:

- Consultation on study-related activities, including guidance and support on study enrolment
- Review feedback from the independent DMC
- Provision of recommendations regarding amendments to the protocol
- Contribution to and oversight of publications and communication of study results.

10.1.6.2 Independent Data Monitoring Committee

Ongoing safety monitoring during the conduct of the study will be performed by an external and independent DMC. An independent statistical analysis center will be involved in processing unblinded safety data for the DMC. Analysis periods and procedures will be defined in an operational charter (DMC charter) filed in the study file. The independent DMC will periodically review and assess safety data from the study for imbalances in an unblinded manner. It is believed that in this way, participant safety can continue to be monitored throughout the duration of the trial, and the integrity of the study maintained. If unexpected safety issues are identified, specific amendments will be implemented based on the recommendation of the DMC. Following data review, the DMC will provide written recommendations that will be transferred to the chairmen of the Steering Committee and Bayer. DMC opinions and recommendations will be notified by Bayer as soon as possible to the competent authorities and the IECs where they qualify for expedited reporting.

10.1.7 Dissemination of Clinical Study Data

Bayer fulfills its commitment to publicly disclose study results through posting the result of the studies on public registries in accordance with applicable law and regulations.

Result Summaries of Bayer's sponsored clinical studies in drug development Phases 2, 3 and 4 and Phase 1 studies in patients are provided in the Bayer Clinical Trials Explorer application after marketing authorization approval in line with the position of the global pharmaceutical industry associations laid down in the "Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases". In addition results of clinical drug trials will be provided on the publicly funded websites ClinicalTrials.gov, and EU Clinical Trials Information System (CTIS) in line with the applicable regulations.

In accordance with the current EU regulations, result summaries will be submitted within one year from the end of the studies in adult populations, or within 6 months for studies in pediatric populations, in all participating countries. No preliminary data analysis (e.g., on EU data only) will be performed, as this might compromise data integrity and the scientific validity of the study. Bayer commits to sharing upon request from qualified scientific and medical researchers patient-level clinical trial data, study-level clinical trial data, and protocols from clinical trials in patients for medicines and indications approved in the United

States (US) and European Union (EU) on or after January 01, 2014 as necessary for conducting legitimate research.

All Bayer-sponsored clinical trials are considered for publication in the scientific literature irrespective of whether the results of the clinical trials are positive or negative.

10.1.8 Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in CRF Completion Guidelines.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents.
- QTLs will be predefined in the integrated data review plan to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during the study and important deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.
- Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.9 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data and its origin can be found in the Source Data Location List or equivalent.

- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The sponsor or designee will perform monitoring to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.10 Study and Site Start and Closure

Study Start

The study start date is the date on which the clinical study will be open for recruitment of participants.

The start of a clinical study in EU is defined as the date on which the first site is declared by the sponsor to be ready to enroll in a country and clinical study will be open for recruitment of participants.

Study/Site Termination

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development
- If the risk-benefit ratio becomes unacceptable owing to, for example
  - Safety findings from this study (e.g., occurrence of AEs for which character, severity or frequency is new, SAEs, clustering of clinically relevant abnormalities in the safety laboratory),
  - Results of preclinical or clinical studies.

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants included earlier than expected.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research

organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.11 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 Appendix 2: Clinical Laboratory Tests

Table 10–1: Protocol-specified Laboratory Tests

Laboratory Tests	Parameters	Laboratory
Clinical chemistry (limited)	Glycated hemoglobin HbA1c Serum creatinine eGFR (CKD-EPI 2009 formula) [a] Serum potassium [a] Uric acid [b] Serum sodium [b]	Central
Urinalysis	Urine albumin-to-creatinine ratio (UACR)	Central
Screening and safety	Serum creatinine eGFR Serum potassium [a] Pregnancy test [c]	Local
Biomarker	For biomarkers whole blood, serum, plasma and urine samples are needed; for urine samples an aliquot will be taken from the morning void samples taken for urinalysis (see Section 8.8 for further information)	Not applicable

CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration, eGFR = estimated glomerular filtration rate, UACR = urine albumin-to-creatinine ratio

a Screening value to be used for eligibility (Section 5.1).

b Uric acid and serum sodium will not be analyzed at Screening.

c In women of childbearing potential. Both serological and urine tests are acceptable and should be performed as required by local regulations.

Sampling for the tests detailed in Table 10–1 will be performed according to the SoA (Section 1.3). Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Investigators must document their review of each laboratory safety report.

In addition to samples for the central laboratory, other blood samples will be taken for screening purposes and for safety for analysis at the local laboratory. These samples may be obtained up to 72 hours before a scheduled visit.

The following local clinical chemistry parameters must be measured for as long as participant is not prematurely discontinued from the study intervention:

- Potassium from blood sample (local)
    - Potassium values should be recorded using a single decimal point (e.g. 4.5 mmol/L or mEq/L)
    - In the event of hyperkalemia, see Section 6.6 for guidance on treatment
- Creatinine from blood sample(local):
  eGFR will be calculated and recorded in the eCRF by the investigator using the CKD-EPI formula.

Up-titration of the study intervention will be based on local potassium and eGFR value and must be documented in the eCRF. Down-titration of the study intervention will occur for safety reasons only (for guidance, see Section 6.6 and Table 6–3).

Estimation of eGFR for central laboratory will be performed using the CKD-EPI formula (Levey et al. 2009):

$$GFR = 141 \times \min(SCr/\kappa, 1)^{\alpha} \times \max(SCr/\kappa, 1)^{-1.209} \times 0.993^{Age} [\times 1.018\ if\ female] [\times 1{,}159\ if\ black]$$

Where SCr is standardized serum creatinine in mg/dL, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of SCr/ κ or 1, and max indicates the maximum of SCr/ κ or 1.

10.3 Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a clinical study participant, associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) associated with the use of study intervention.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- Sign, symptoms, or the clinical sequelae of suspected medication errors, misuse and abuse of either study intervention or a concomitant medication. Medication errors, misuse and abuse per se will not be reported as an AE/SAE, unless it is resulting in AE/SAE. Such medication errors, misuse and abuse should be reported regardless of sequelae.
- Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events <u>NOT</u> Meeting the AE Definition

- Any abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition

- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2 Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets the one or more of the criteria listed:

a. **Results in death**

b. **Is life threatening**

- The term *life threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. **Requires inpatient hospitalization or prolongation of existing hospitalization**

- In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. **Results in persistent or significant disability/incapacity**

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. **Is a congenital anomaly/birth defect**

f. **Other situations:**

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

10.3.3 Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to Sponsor in lieu of completion of the required form.
- There may be instances when copies of medical records for certain cases are requested by Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

- The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:
  - Mild: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
  - Moderate: A type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
  - Severe: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.

- For causality assessment, the investigator will also consult the IB and/or product information, for marketed products.
- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes. There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to Sponsor . However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission** of the SAE data to Sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Sponsor with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to Sponsor within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

SAE Reporting to Sponsor via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to Sponsor will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data transmission (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the medical monitor by telephone.
- Contacts for SAE reporting can be found in the investigator site file.

SAE Reporting to Sponsor via Paper Data Collection Tool

- Email transmission of the SAE paper data collection tool is the preferred method to transmit this information to the Sponsor.
- In rare circumstances and if email transmission is not feasible, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE data collection tool within the designated reporting timeframes.
- Contacts for SAE reporting can be found in the investigator site file.

10.4 Appendix 4: Contraceptive and Barrier Guidance

10.4.1 Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

Women in the following categories are considered WOCBP (fertile)

1. Following menarche
2. From the time of menarche until becoming postmenopausal unless permanently sterile (see below):
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
        - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement > 40 mIU/mL (for US only: FSH levels > 40 mIU/mL and estradiol < 20 pg/mL) is required.
        - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.
    - Permanent sterilization methods (for the purpose of this study) include:
        - Documented hysterectomy
        - Documented bilateral salpingectomy
        - Documented bilateral oophorectomy
        - For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Woman of Nonchildbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

1. Premenopausal female with permanent infertility due to one of the following:
    a) Documented hysterectomy

b) Documented bilateral salpingectomy

c) Documented bilateral oophorectomy

d) For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview

2. Postmenopausal female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement >40 mIU/mL (for US only: FSH levels >40 mIU/mL and estradiol <20 pg/mL) is required.
    - Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.2 Contraception Guidance

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency *Failure rate of < 1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[c]
• Bilateral tubal occlusion
• Azoospermic partner (vasectomized or due to a medical cause) *Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.* Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Methods[b] That Are User Dependent *Failure rate of < 1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] – oral – intravaginal – transdermal – injectable
Progestogen-only hormone contraception associated with inhibition of ovulation[c] – oral – injectable
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*
Effective Methods[d] That Are Not Considered Highly Effective *Failure rate of ≥ 1% per year when used consistently and correctly.*
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action
• Male or female condom with or without spermicide
• Cervical cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]
a) Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b) Failure rate of < 1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c.) Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. d) Considered effective, but not highly effective - failure rate of ≥ 1% per year. Note: Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure from friction).

10.5 Appendix 5: Genetics

Whole genome sequencing (WGS) will be offered to all participants. The WGS analysis will only be carried out in samples from those participants who have provided respective optional informed consent. Participants who do not wish to have their sample(s) analyzed for WGS may still participate in the study.

Details on sample handling will be provided separately.

See Section 8.8 for further details.

10.6 Appendix 6: Calculating the Child Pugh score

The severity of liver disease (Table 10–2) will determine the Child Pugh score (Table 10–3).

Table 10–2: Grading of severity of liver disease, adapted from (Pugh et al. 1973)

Factor	+1	+2	+3
Bilirubin (mg/dL)	<2	2 – 3	>3
Albumin (g/dL)	>3.5	2.8 – 3.5	<2.8
International Normalized Ratio	<1.7	1.7 – 2.3	>2.3
Ascites	None	Mild	Moderate / Severe
Encephalopathy	None	Grade I – II	Grade III – IV

Table 10–3: Classification using the added score from Table 10–2, adapted from (Pugh et al. 1973)

Child-Pugh Class	A	B	C
Points	5 – 6	7 – 9	10 – 15

10.7 Appendix 7: Country-specific Requirements

10.7.1 China (CHN)

China:

- Whole genome sequencing will not be performed.
- Genetic biomarker samples will not be performed.
- Laboratory sample leftovers must not be repurposed after measurement.
  Central laboratory: Labcorp Pharmaceutical Research and Development (Shanghai) Co., Ltd
  Central sample destruction facility: Shanghai Solid Waste Disposal Center.

10.7.2 Denmark (DNK)

- Whole genome sequencing will not be performed.
- Genetic biomarker samples will not be performed.
- Local laboratory method is specified as being *plasma* K^+, creatinine and pregnancy test.

10.7.3 Republic of Korea (KOR)

- Serum pregnancy test must be available before randomization.
- Regular pregnancy test (urine or serum) is required at Visit 4, Visit 5 and premature discontinuation.

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